



PATENT COOPERATION T





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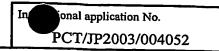
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

	(PCT Article	36 and Rule 70)	
Applicant's or agent's file reference 104F1002 FOR FURTHER A		CTION	See Form PCT/IPEA/416
International application No. International filing d PCT/JP2003/004052 28 March 200		te (day/month/year) 3 (28.03.2003)	Priority date (day/month/year) 23 October 2002 (23.10.2002)
International Patent Classification (IPC) or n A61K 38/17, 9/19, 35/12, 47/36,	ational classification and A61L 27/22, 27/38,	d IPC A61P 41/00	· · · · · · · · · · · · · · · · · · ·
Applicant	INOUE, F	Kazutomo	
Authority under Article 35 and trans	smitted to the applicant	according to Article 36	
2. This REPORT consists of a total of		_	heet.
3. This report is also accompanied by A			
a (sent to the applicant and	to the International Bu	reau) a total of	sheets, as follows:
sheets of the desc and/or sheets cont Administrative In	taining rectifications au	rawings which have be thorized by this Autho	een amended and are the basis of this report rity (see Rule 70.16 and Section 607 of the
sheets which super beyond the disclo Supplemental Box	sure in the internationa	t which this Authority l application as filed, a	considers contain an amendment that goes as indicated in item 4 of Box No. I and the
b. (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			and/or tables related thereto, in computer
4. This report contains indications relat	ting to the following ite	ms:	
Box No. I Basis of the re	port		
Box No. II Priority			· ·
Box No. III Non-establishr	ment of opinion with re	gard to novelty, invent	ve step and industrial applicability
Box No. IV Lack of unity of	of invention		
Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement			
Box No. VI Certain docum			
Box No. VII Certain defects in the international application			
Box No. VIII Certain observ	ations on the internation	nal application	
Date of submission of the demand		Date of completion of this report	
15 March 2004 (15.03.2	2004)	09 November 2004 (09.11.2004)	
Name and mailing address of the IPEA/JP		Authorized officer	
Facsimile No.		Telephone No.	

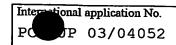
Box N	0. I	Basis of the report
1. Wit	h regare erwise in	to the language, this report is based on the international application in the language in which it was filed, unless
	This which	report is based on translations from the original language into the following language, this language of a translation furnished for the purpose of:
1		international search (under Rules 12.3 and 23.1(b))
		publication of the international application (under Rule 12.4)
		international preliminary examination (under Rules 55.2 and/or 55.3)
		(
2. With furn and	are not	I to the elements of the international application, this report is based on (replacement sheets which have been the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" annexed to this report): atternational application as originally filed/furnished
		scription:
	pages	
i	pages	, as originally filed/furnished
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	the cla	
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	pages pages	, as originally filed/furnished
	pages'	, as amended (together with any statement) under Article 19
	pages'	leceived by this Authority on
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	pages	, as originally filed/furnished
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	a seque	ence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3.	The an	nendments have resulted in the cancellation of:
		he description, pages
	_	he claims, Nos.
	=	
	H	he drawings, sheets/figs
	H	the sequence listing (specify):
	• لــا	ny table(s) related to sequence listing (specify):
4. 🔲	(Rule 7	port has been established as if (some of) the amendments annexed to this report and listed below had not been since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box 0.2(c)).
	<u> </u>	de description, pages
	∐ tt	e claims, Nos.
	th	e drawings, sheets/figs
	th	e sequence listing (specify):
	☐ ar	ny table(s) related to sequence listing (specify):
		co sequence noting (specify):
* If item	4 applie	es, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMENTAL RY REPORT ON PATENTABILITY



Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrial applicable have not been examined in respect of:
the entire international application.
Claims Nos
because:
the said international application, or the said claims Nos
See supplemental sheet
the description, claims or drawings (indicate particular elements below) or said claims Nosare so unclear that no meaningful opinion could be formed (specify):
the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed.
no international search report has been established for said claims Nos
the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
the written form has not been furnished
does not comply with the standard
the computer readable form has not been furnished
does not comply with the standard
the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
see Supplemental Box for further details.





Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

Claims 5 and 8-19 pertain to methods for treatment of the human body by therapy, and thus relate to subject matter which does not require international preliminary examination by this International Preliminary Examining Authority, under the provisions of PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

INTERNATIONAL PRELICENCY REPORT ON PATENTABILITY

In	ional application No.
	PCT/JP2003/004052

Box No. IV	Lack of unity of invention	_
		
	response to the invitation to restrict or pay additional fees the applicant has:	
	paid additional fees.	
	paid additional fees under protest.	
	neither restricted nor paid additional fees.	
2. not	Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, to invite the applicant to restrict or pay additional fees.	
3. This Author	ority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is	
	olied with.	
	omplied with for the following reasons:	
See	supplemental sheet	i
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Consequently	, this report has been established in respect of the following parts of the international application:	
	parts.	
🛭 th	e parts relating to claims Nos	

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV. 3.

Claims 1-4 relate to angiogenesis inducers containing fibrin.

Claims 6-7 relates to particulate preparations obtained by freeze-drying fibrin.

Claims 1-4 and 6-7 have in common preparations containing fibrin; however, preparations containing fibrin are disclosed for example in document WO 00/38752 A and are, therefore, not novel. This common feature is thus not a special technical feature in the sense of the second sentence of PCT Rule 13.2.

Claims 1-4 and 6-7 thus do not satisfy the condition of unity of invention.

INTERNATIONAL PRE NARY EXAMINATION REPORT

Internat	ional	application No.
P	JP	03/04052

V .	Reasoned statement under Article 35(2) with regard to no citations and explanations supporting such statement	velty, inventive step or industrial applicability;
1.	Statement	

1.	Statement			
	Novelty (N)	Claims		YES
		Claims	1-4, 6-7	NO
	Inventive step (IS)	Claims		YES
		Claims	1-4, 6-7	NO
	Industrial applicability (IA)	Claims	1-4, 6-7	YES
		Claims		NO

2. Citations and explanations

Documents

Documents cited in the international search report

- WO 00/62833 A (The Research Foundation of State University of New York), 26 October 2000
- 2. US 2002/150879 A (Eugene A. Woltering et al.), 17
 October 2000
- 3. JP 2002-506344 A (Fidio Advanced Biopolymers SRL), 26 February 2002
- 4. WO 00/64376 A (C. R. Bard, Inc.), 2 November 2000
- 5. JP 2000-119194 A (Hiroko Yanaga), 25 April 2000

Documents cited for the first time here

- 6. C. Okubo et al., "Seitai kenbikyou-teki ni kansatsushita soushou chiyu katei" Dai 21 Kai Sosho Chiyu Kenkyukai, 1992, vol. 12, no. 11, pp. 2907-2913
- 7. H. Okamoto et al., "b-FGF wo kanwashita 'fibrin' nori 'sheet' ga hiben-nai kekkan-kei ni oyobosu eikyou", Dai 22 Kai Sosho Chiyu Kenkyukai, 1993, vol. 13, no. 11, pp. 2612-2614
- 8. JP 6-199685 A (E. R. Squibb & Sons, Inc.), 19 July 1994 & AT 244581 A & AU 676201 B2 & AU 4887893 A & BR 9304185 A & CA 2108104 A1 & CN 1091315 A & CZ 9302117 A3 & DE 69333080 D1 & DE 69333080 A & DK 592242 A &

EP 0592242 A1 & EP 1266666 A2 & ES 2065294 A1 & ES 2202306 A & FI 934440 A & HU 66587 A2 & IL 107211 A & MX 9306272 A1 NO 933624 A

9. JP 61-178927 A (Serapharm GmbH & Co. KG), 11 August 1986 & AT 13810 A & AT 20824 A & DE 3171072 D1 & DE 3175003 D1 & EP 68047 A2 & EP 68048 A2 & EP 68149 A2 & JP 58-038216 A & JP 58-38217 A & JP 58-36545 A & US 4427650 A & US 4427651 A & US 4442655 A

Explanations

The inventions set forth in claims 1-4 are not novel and do not involve an inventive step in the light of document 1.

Document 1 (see claims 12-16 and 19 and example II, III and V, etc.) discloses an angiogenesis device which includes cells, microcarrier particles (dextran or the like) and a fibrin matrix, and also mentions the addition of a growth factor to the aforementioned device.

The inventions set forth in claims 1 and 3-4 are not novel and do not involve an inventive step in the light of document 2.

Document 2 (see claims 14-18 and 23-24, etc,) discloses the fact that when tissue is embedded in a matrix comprising fibrin and cultured after adding a medium which includes a growth factor, angiogenesis is produced.

The inventions set forth in claims 1-3 are not novel and do not involve an inventive step in the light of document 3.

Document 3 (see claims 1, 19 and 23-25, etc.) discloses biological material which includes cells including endothelial cells, hyaluronic acid and collagen (polymers degradable in the body), and fibrin, for use in surgery in order to enhance the biological process of angiogenesis of tissue.

d. The inventions set forth in claims 1-2 and 4 are not novel and do not involve an inventive step in the light of document 4.

Document 4 (see claims 21-22; page 8, lines 12-22; page 17, lines 2-3; page 17, lines 19-27; and page 19, lines 1-14) discloses a method for promoting revascularization, which comprises transplanting into the tissue a blood clot (fibrin) formed from blood outside the body; it also mentions the possibility of transplanting the blood clot (fibrin) and a growth factor into tissue together with a biodegradable material.

e. The invention set forth in claim 1 is not novel and does not involve an inventive step in the light of document 5.

Document 5 (see claims 1 and 2 and paragraphs [0014] and [0008], etc.) discloses an agent comprising fibrin for promoting production of TGF- α and/or TGF- β , and promotion of production of TGF- β in epithelial cells and fibroblast cells in a culture medium with added fibrin (fibrinogen preparation BeriplastP), and mentions that angiogenesis was seen and repair of tissue injury occurred rapidly after topical administration of TGF- β .

f. The invention set forth in claim 1 is not novel and does not involve an inventive step in the light of document 6.

Document 6 (page 300, right column) discloses the fact that when a tissue adhesive (Beriplast) was applied to a transparent window placed in the ear (rabbit ear

chamber; REC) in order to observe the microcirculation, the structure of the microvascular network inside the REC was good.

g. The invention set forth in claim 4 is novel and does not involve an inventive step in the light of newly cited document 7.

Document 7 (page 177, methods and results) states that in a group of rats in which a fibrin glue sheet was placed on the surface of an isolated skin flap made on the abdominal fascia, no marked change was noted in the vasculature within the skin flap; however, marked angiogenesis was noted in the group in which a sheet of fibrin glue mixed with b-FGF was similarly placed.

h. The invention set forth in claim 1 is not novel and does not involve an inventive step in the light of newly cited document 8.

Document 8 (see claims 1, 32, 59 and 60, and paragraphs [0113] and [0128], etc.) discloses a method of using a fibrin sealant wherein the desired site is brought into contact with a composition containing fibrin monomer, which is converted into fibrin polymer to form a fibrin sealant, discloses a method for producing a composition containing fibrin monomer from fibrinogen, characterized by solubilizing a non-crosslinked fibrin polymer obtained by bringing a fibrinogen-containing composition into contact with a thrombin-like enzyme, gives applications of aforementioned compositions such as suturing of tissues and organs, treatment of wounds and sealing of sites after surgery, indicates that when the desired site includes blood and a composition containing fibrin monomer is used, a fibrin sealant can be formed without employing another composition (diluent or alkaline buffer) because the fibrin monomer is converted into fibrin polymer by the

blood.

Given the aforementioned disclosures, document 8 can be considered to disclose particulate freeze-dried preparations which comtain fibrin monomer obtained by bringing fibrinogen into contact with a thrombin-like enzyme, and the fact that an aforementioned particulate freeze-dried preparation functions as an adhesive when brought into contact with a site of surgery or tissue which includes blood.

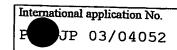
Document 8 does not disclose angiogenesis inducers; however, the description of the present application mentions application to wounds as an application of the angiogenesis inducers, and since it is evident from the description of the aforementioned applications that the compositions containing fibrin monomer disclosed in document 8 can also be used for application to wounds, the angiogenesis inducers claimed in claim 1 are indistinguishable from the invention disclosed in document 8 in this regard.

The inventions set forth in claims 6-7 are not novel and do not involve an inventive step in the light of newly cited document 8.

In addition to the items mentioned above in h., document 8 (see claims 59 and 60 and paragraphs [0107] and [0128], etc.) discloses solid compositions containing fibrin monomer, formed by freeze-drying an aqueous solution containing fibrin monomer; it also mentions that the freeze-dried fibrin monomer can be granular, and that when the desired site includes blood and a composition containing fibrin monomer is used, a source of supply of calcium ions is ideally added to the solution used in the solubilization step.

The invention set forth in claim 6 does not involve

INTERNATIONAL PREMINARY EXAMINATION REPORT



an inventive step in the light of newly cited document 9.

Document 9 (see claims 1, 8-10 and 12, etc.) discloses a method for producing a freeze-dried preparation by freeze drying fibrin formed by the action of thrombin on fibrinogen, and cutting the freeze-dried preparation taken from the freezing die to give the moulded shape.

Document 9 does not disclose the shapes of the freeze-dried preparation; however, the shape of a preparation is merely a matter of design which can be decided at the discretion of a person skilled in the art; and a person skilled in the art could easily make the preparation particulate.

k. The invention set forth in claim 7 does not involve an inventive step in the light of document 9.

Addition of calcium when obtaining fibrin from fibrinogen and thrombin is known in this technical field.

1. The inventions set forth in claims 1-4 and 6-7 are industrially applicable.

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